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Original Article

Independent association of obstructive sleep apnea with left ventricular geometry and systolic function in resistant hypertension: the RESIST-POL study

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ABSTRACT

Objective: We investigated the impact of obstructive sleep apnea (OSA) and night blood pressure (BP) on left ventricular geometry and systolic function in patients with resistant hypertension (RHTN).
Methods and Results: Data from 155 patients with RHTN were analyzed. All patients underwent biochemical evaluations, ambulatory blood pressure monitoring (ABPM), and polysomnography. Left ventricular mass index (LVMI), relative wall thickness (RWT), left ventricular ejection fraction (LVEF), midwall fractional shortening (mwFS) and global longitudinal strain (GLS) were measured. Patients were divided into four groups based on the presence of metabolic syndrome (MS) and OSA: group 1: OSA(–), MS(–) [$n = 42$]; group 2: OSA(+), MS(–) [$n = 14$]; group 3: OSA(–), MS(+) [$n = 46$]; and group 4: OSA(+), MS(+) [$n = 53$]. In group 3 and 4 concentric geometry was present in 53.2% and 79.6% respectively ($P = 0.004$). There were no differences in LVEF between groups. Group 3 and 4 had lower mwFS as compared with group 1 (16.40 ± 1.9 and 15.38 ± 2.2 vs 17.44 ± 1.9; $P < 0.049$ and $P < 0.0001$ respectively). Group 4 had significantly lower GLS as compared with group 1 (-12.64 ± 3.3 vs -15.59 ± 4.0; $P < 0.001$). In the multivariable analysis, factors independently associated with concentric geometry were age, nighttime SBP (OR –1.04; 95%CI 1.019–1.082; $P < 0.0001$) and OSA (OR –3.97; 95%CI 1.835–8.590; $P < 0.0001$). In the other multivariable analysis, factors independently associated with GLS were OSA (beta = 0.279; $P = 0.001$), and nighttime DBP (beta = 0.168; $P = 0.048$) whereas factors independently associated with mwFS were age, gender, nighttime SBP, concentric geometry, and metabolic syndrome.
Conclusions: In patients with true RHTN without diabetes concentric geometry and systolic dysfunction are independently associated with moderate and severe OSA and nighttime BP levels.

1. Introduction

Resistant hypertension (RH), occurring in 12–13% of treated hypertensive subjects, is of major clinical importance since it has been associated with higher cardiovascular risk [1,2]. It has also been shown that patients with RH are characterized by high incidence of target-organ damage, including left ventricular hypertrophy and concentric geometry [3–5].

The most frequently associated condition found in patients with RH is obstructive sleep apnea (OSA), often overlapping with metabolic syndrome (MS) [6]. Concentric geometry is associated with poor prognosis [7]. Several studies have shown that structural changes of left ventricular hypertrophy and concentric geometry are often found in patients with OSA [8,9].

In contrast to studies based on the assessment of left ventricular systolic function by means of ejection fraction [10], studies using speckle-tracking echocardiography (STE) have demonstrated that OSA patients may develop subclinical left ventricle systolic dysfunction [11,12].

We hypothesized that the high frequency of cardiac structure alteration in patients with RH might be related to common coexistence of OSA. We also evaluated whether this relationship is independent of blood pressure levels and frequently overlapping

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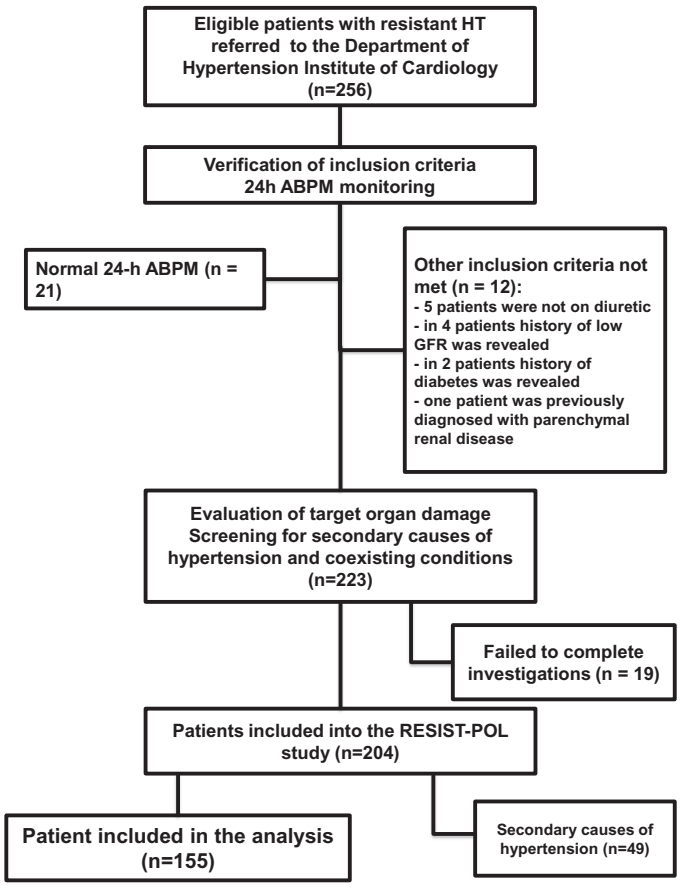

Fig. 1. Flow chart of the study population. HT, hypertension; ABPM, ambulatory blood pressure monitoring; GFR, glomerular filtration rate.

metabolic syndrome. Additionally, we evaluated the impact of OSA in patients with RH on systolic function, employing assessment of more accurate markers of systolic function such as midwall fractional shortening (mwFS) and global longitudinal strain (GLS).

2. Methods

2.1. Study population

Patients were enrolled in the RESIST-POL study in the Department of Hypertension, Institute of Cardiology, Warsaw, Poland between 2009 and 2011. The RESIST-POL study, based on the evaluation of 204 patients with RH, showed a high incidence of OSA and MS. The study revealed that different secondary causes of hypertension, including primary aldosteronism, renal artery stenosis, hyperthyroidism, and renal artery aneurysm were diagnosed in 49 patients (Fig. 1). Since the principle goal of the present study was to evaluate the relationship between OSA and left ventricle morphology and function in patients with RH, all cases with secondary causes of hypertension characterized by other underlying mechanisms that may independently influence the left ventricle structure and blood pressure pattern were ruled out. The inclusion criteria were as follows: age 20–65 years, and RH confirmed in 24 h ambulatory blood pressure monitoring (ABPM) [mean daytime blood pressure (BP) > 135/85 mmHg] while on three antihypertensive drugs in optimal doses (including diuretic). The exclusion criteria were: a history of other cardiovascular diseases (ischemic heart disease, heart failure, transient ischemic attacks and previous stroke), secondary causes of RH (for the purpose of this analysis), decreased estimated glomerular filtration rate <60 mL/min per 1.73 m^2), neoplastic diseases, previous diagnosis of diabetes mellitus, alcohol or medicine addictions, advanced changes in the skeletal system, malignant hypertension, pregnancy, and lack of cooperation or agreement to participation in the study.

It should be emphasized that the analyzed group consists only of patients without factors that may potentially alter morphology and function of the left ventricle, especially in patients with type 2 diabetes mellitus. Therefore patients included in our analysis were characterized as newly diagnosed, never-treated OSA, and by being free of diabetes, severe cardiovascular disorders, chronic kidney disease, and secondary causes of hypertension, thus limiting the influence of other factors on the evaluated relationship between OSA and cardiac structure and function.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. It was approved by the local Research Ethics Committee. Written informed consent was also obtained from each patient.

The full protocol and main results of the RESIST-POL study have been already published. In brief, patients with true RH were screened for coexisting conditions including metabolic abnormalities and OSA, secondary causes of hypertension as well as evaluated for target organ damage. As the methodology of the RESIST-POL study has been described previously, we summarize below the definitions and methods used for the purpose of this analysis [13].

2.2. Office blood pressure measurements

Blood pressure was measured by a trained nurse with a patient in the sitting position after a 5 min rest, using an automated device (Omron 705IT, Omron Co., Kyoto, Japan). Based on the upper arm circumference, an appropriately sized cuff was placed on the arm with the lower edge of the cuff 2 cm above the antecubital fossa. Three consecutive readings were performed. In cases where the difference between readings was >10 mmHg, further measurements were taken so as to obtain three consecutive consistent readings, the average of which was then recorded.

2.3. Ambulatory blood pressure monitoring

In all patients, the ABPM was recorded using Spacelabs 90207 or 90217 (Redmond, WA, USA). Readings were obtained every 15 min during the day (06:00–22:00) and every 30 min during the night (22:00–06:00). Average 24 h, daytime and night-time systolic blood pressure (SBP), daytime and night-time diastolic blood pressure (DBP), and average 24 h heart rate (HR) were analyzed. The nocturnal decrease in BP was quantified as the relative decrease in nocturnal BP for both systolic and diastolic BP: [(daytime pressure – night-time pressure)/daytime pressure] × 100 and expressed as a percentage.

2.4. Polysomnography

All patients irrespective of the symptoms of OSA were evaluated by standard polysomnography with an Alice 5 (Respironics Inc., Murrysville, PA, USA) device. The polysomnographic recordings were scored manually using 30 s epochs following Rechtschaffen and Kales' criteria for sleep and wake determination and sleep staging. Abnormal respiratory events were evaluated according to the standard criteria of the American Academy of Sleep Medicine Task Force [14]. Apnea–hypopnea index (AHI) indicating the number of apneic and hypopneic episodes per hour of sleep was calculated. Clinically significant OSA was diagnosed when AHI was >15.

2.5. Metabolic syndrome

Metabolic syndrome was diagnosed if three of five of the following criteria were present: (1) BP ≥130/85 mmHg: this criterion was met in all patients; (2) abdominal obesity: waist circumference, males >102 cm, females >88 cm; (3) high-density lipoprotein (HDL)-cholesterol, males <40 mg/dL, females <46 mg/dL; (4) triglycerides >150 mg/dL; and (5) fasting plasma glucose ≥100 mg/dL [15]. Aldosterone and sodium excretion were assessed using a 24 h urine collection. Biochemical evaluation of blood samples was performed after overnight fasting.

2.6. Echocardiography

All patients underwent a complete transthoracic echocardiographic study with a GE Medical System Vivid 7 (GE Healthcare) with a 2.5 MHz transducer. M-mode, two-dimensional (2D) tissue Doppler echocardiography and speckle-tracking techniques were used. The values of all echocardiographic parameters were obtained as the average of three consecutive cardiac cycles. Left ventricular end-systolic (*LVESd*) and end-diastolic (*LVEDd*) diameters, as well as interventricular septal diastolic diameter (*IVSDd*) and posterior wall diastolic diameter (*PWDd*) were measured according to the American Society of Echocardiography recommendations using the M-mode technique [16].

Left ventricular mass (*LVM*) was calculated using the following formula:

$$LVM\,(\mathrm{g}) = 0.8 \times \left[1.04\,(LVEDd + PWDd + IVSDd)^3 - (LVEDd)^3\right] + 0.6.$$

Left ventricular mass index (LVMI) was obtained by normalizing *LVM* to body surface area (BSA). Left ventricular hypertrophy was defined as LVMI ≥110 g/m^2 for women and ≥125 g/m^2 for men. Relative wall thickness (RWT) was calculated as (*IVSDd* + *PWDd*)/*LVEDd*. Concentric geometry was defined as RWT >0.45 [17]. LVMI and RWT were used to differentiate four types of left ventricular geometry: normal geometry (RWT ≤0.45 and normal LVMI), concentric remodeling (RWT >0.45 and normal LVMI), concentric hypertrophy (RWT >0.45 and increased LVMI), and eccentric hypertrophy (RWT ≤0.45 and increased LVMI).

Left ventricular systolic function was evaluated by left ventricular ejection fraction (LVEF), *mwFS*, and longitudinal strain. LVEF was calculated using biplane Simpson formula. *mwFS* was estimated as follows [18]:

$$Inner\ shell = \left[(LVEDd + IVSd/2 + PWDd/2)^3 - LVEDd^3 + LVESd3\right]^{1/3} - LVESd$$

$$mwFS = \frac{\left(\left[LVEDd + \frac{IVSD}{2} + \frac{PWDd}{2}\right] - [LVEDs + inner\ shell]\right)}{\left(LVEDd + \frac{IVSd}{2} + \frac{PWDd}{2}\right)} \times 100$$

For the left ventricle longitudinal strain evaluation, an apical four-chamber view was obtained. Three consecutive end-expiratory cycles, in grayscale (frame rate = 60–70 frames/s), were stored for one of the apical views and subsequently transferred to an EchoPac workstation (EchoPac version BT09, GE Healthcare). The analysis of 2D strain was performed offline by semi-automatic tracking of the left ventricle. After manually tracking the endocardial border on a 2D image end-systolic frame, the software automatically tracked myocardial motion, creating six equidistant speckle-tracking regions of interest. Longitudinal LV strain was defined as the average of negative strains of six segments of the septal and lateral walls in the apical four-chamber view.

2.7. Statistical analysis

All data are expressed as mean ± standard deviation and frequency as a percentage. Significant differences of the studied parameters between the four groups were determined by means of the analysis of variance (ANOVA). Multiple comparisons between the four groups were performed by one-way ANOVA with the Duncan and Bonferroni post-hoc test. Categorical variables were compared with χ^2-test. Pearson's correlation was used to investigate the correlation of variable factors with echocardiographic parameters. All statistical analyses were performed with commercially available computer software PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Parameters identified as statistically significant based on univariate analysis ($P < 0.05$) were included in the multivariate logistic and linear regression models in order to determine the combined effect of several variables on the evaluated echocardiographic parameters. $P < 0.05$ was considered statistically significant.

3. Results

In all, 155 patients were analyzed. The mean age of the study subjects was 47.5 ± 10.5 (range, 19–65; 92 males and 63 females). Clinically significant OSA was diagnosed in 67 patients (43.2%) and metabolic syndrome was found in 99 patients (63.9%). Patients were divided into four groups based on the presence of OSA and MS: group 1, OSA$^-$/MS$^-$ ($n = 42$); group 2, OSA$^+$/MS$^-$ ($n = 14$); group 3, OSA$^-$/MS$^+$ ($n = 46$); and group 4, OSA$^+$/MS$^+$ ($n = 53$). Considering the metabolic parameters, the total and LDL-cholesterol levels were similar in all four groups, whereas fasting plasma glucose and triglycerides were significantly higher and HDL-cholesterol lower in groups 3 and 4 compared with group 1. There were no differences in aldosterone serum concentration between the four analyzed groups. The median number of antihypertensive drugs was four and individual antihypertensive medication drug classes were prescribed with the following frequencies in the whole group: thiazide/loop diuretics, 97.5%; calcium channel blockers, 82.8%; β-blockers, 77.9%; angiotensin-converting enzyme inhibitors, 63.2%; angiotensin II receptor blockers, 55.8%; α-blockers, 38.6%; centrally acting drugs, 11.6%; spironolactone, 8.6% (no patient was receiving eplerenone). There were no significant differences in frequency of antihypertensive drugs classes between analyzed groups, nor were there significant differences in office and ambulatory BP levels between the groups (Table 1).

Patients from groups 2, 3, and 4 had greater IVSDd, PWDd, and higher RWT compared with those from group 1. Group 4 had significantly greater IVSDd, PWDd, and higher RWT compared with group 3. No significant differences in LVMI between the groups were found. Left ventricular hypertrophy (LVH) was found in 72 patients (46.5%), the majority of whom were in groups 2 and 4 (Table 2).

Significant differences in the prevalence of four types of left ventricular geometry were observed (Fig. 2). In group 4, LVH was found in 59.3%, whereas abnormal geometry was found in 92.6%. Normal geometry was most prevalent in group 1, whereas concentric geometry (concentric remodeling and concentric hypertrophy) was most prevalent in group 2 and 4 (71.5% and 79.6%, respectively).

None of the patients had segmental wall motion abnormalities; in all patients, ejection fraction was within normal limits. There were no differences in LVEF between the groups. Groups 3 and 4 were characterized by lower mwFS compared with group 1. Group 4 had significantly lower GLS compared with group 1. mwFS and GLS were the lowest in group 4 (Table 2).

In the whole group, AHI significantly correlated with: LVMI ($r = 0.282$, $P = 0.001$), RWT ($r = 0.335$, $P = 0.0001$), and GLS ($r = 0.244$, $P = 0.006$), and significantly negatively correlated with mwFS ($r = -0.302$, $P = 0.0001$). Night-time SBP was correlated with LVMI ($r = 0.371$, $P = 0.0001$), RWT ($r = 0.301$, $P = 0.0001$), and mwFS

Table 1
Demographic and clinical characteristics of the study groups.

Variables	Group 1 ($n = 42$)	Group 2 ($n = 14$)	Group 3 ($n = 46$)	Group 4 ($n = 53$)	ANOVA
Age (years)	43.7 ± 10.9	51.1 ± 12.5[a]	46.7 ± 10.5	50.1 ± 8.6[b]	0.012
Sex (F/M)	26/16	1/13	26/20	9/44	<0.0001
Body mass index (kg/m^2)	26.7 ± 5.0	29.3 ± 3.2	30.3 ± 3.5[c]	32.4 ± 4.3[b]	0.022
Body surface area (m^2)	1.89 ± 0.24	2.09 ± 0.16	2.07 ± 0.20	2.18 ± 0.18	<0.0001
Known history of hypertension (years)	10.4 ± 9.2	12.3 ± 9.4	9.8 ± 8.0	11.3 ± 8.3	0.72
Median no. of antihypertesive drugs (interquartile range)	4 (3–5)	4 (3–5)	5 (4–6)	4 (3–5)	0.21
Creatinine (μmol/L)	73.2 ± 17.7	74.8 ± 12.8	77.1 ± 15.1	86.1 ± 19.0[b,d]	0.002
GFR (mL/min/1.73 m^2)	94.6 ± 20.4	103.4 ± 18.5	88.4 ± 16.7	87.2 ± 19.8	0.018
Abdominal obesity (%)	31.0	60.0[a]	87.5[c]	94.4[b]	<0.0001
IFPG (%)	11.9	20.0	75.0[c]	74.1[b]	<0.0001
HDL-C (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	1.2 ± 0.4[c]	1.1 ± 0.3[b]	<0.0001
Triglyceride (mmol/L)	1.3 ± 0.5	0.9 ± 0.3	1.9 ± 1.4[c]	2.0 ± 0.9[b]	<0.0001
Total cholesterol (mmol/L)	5.4 ± 1.0	4.8 ± 1.5	5.1 ± 1.3	5.1 ± 1.0	0.41
LDL-C (mmol/L)	3.3 ± 0.9	3.3 ± 1.4	3.2 ± 1.1	3.4 ± 0.9	0.79
Aldosterone 24 h urine excretion (μg/24 h)	19.6 ± 11.9	17.9 ± 5.4	19.4 ± 10.6	20.8 ± 9.4	0.77
24 h urinary sodium excretion (mEq/24 h)	144.7 ± 66.0	199.3 ± 76.6	182.3 ± 74.2	188.5 ± 85.1	0.02
AHI (events/h)	5.6 ± 4.5	36.9 ± 18.4[a]	7.0 ± 5.0	40.4 ± 23.9[b,d]	<0.0001
Mean saturation (%)	95.7 ± 1.8	93.9 ± 1.9[a]	94.8 ± 1.4	93.1 ± 2.0[b,d]	<0.0001
Office SBP (mmHg)	157.9 ± 23.0	162.9 ± 23.9	159.1 ± 23.6	159.0 ± 19.1	0.92
Office DBP (mmHg)	94.4 ± 15.2	94.3 ± 11.9	95.6 ± 14.7	98.9 ± 15.2	0.54
24 h SBP (mmHg)	135.3 ± 17.3	139.4 ± 12.4	140.6 ± 20.6	138.7 ± 16.4	0.56
24 h DBP (mmHg)	84.7 ± 11.9	83.5 ± 11.5	85.5 ± 14.4	86.4 ± 12.1	0.86
Daytime SBP (mmHg)	140.8 ± 17.5	143.2 ± 13.2	146.0 ± 22.3	143.2 ± 17.6	0.64
Daytime DBP (mmHg)	89.4 ± 12.3	87.0 ± 12.0	88.7 ± 14.8	90.5 ± 12.5	0.81
Night-time SBP (mmHg)	124.2 ± 18.3	132.2 ± 11.5	131.4 ± 20.2	129.2 ± 15.5	0.58
Night-time DBP (mmHg)	76.4 ± 12.6	77.2 ± 11.3	77.7 ± 13.5	79.1 ± 10.5	0.77
Non-dippers, SBP (beats/min)	41.5	71.4	58.7	48.0	0.17
Non-dippers, DBP (beats/min)	29.3	42.9	28.9	38.0	0.62
24 h heart rate (beats/min)	68.9 ± 10.2	64.2 ± 8.8	68.7 ± 9.9	69.6 ± 8.8	0.34

Abbreviations: ANOVA, analysis of variance; GFR, glomerular filtration rate; IFPG, increased fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; AHI, apnea–hypopnea index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values are mean ± standard deviation, except for categorical variables.
[a] $P < 0.05$ group 2 vs group 1.
[b] $P < 0.05$ group 4 vs group 1.
[c] $P < 0.05$ group 3 vs group 1.
[d] $P < 0.05$ group 3 vs group 4.

($r = -0.299$, $P = 0.0001$). Additionally, a significant correlation was noted between night-time DBP and GLS ($r = 0.191$, $P = 0.030$), mwFS ($r = -0.309$, $P = 0.0001$), and RWT ($r = 0.244$, $P = 0.002$). There were significant correlations between office SBP and DBP, daytime and 24 h SBP, and DBP and GLS, mwFS, and LVMI. However, these correlations were weaker than for night-time SBP and DBP, and between nocturnal fall of SBP ($r = -0.138$, $P = 0.09$) and DBP ($r = -0.142$, $P = 0.08$) with LVMI they were not significant.

To evaluate independent factors related to concentric geometry of left ventricle and systolic function parameters (mwFS and GLS), logistic and linear regression models were performed. In the multivariate logistic regression model, the factors independently associated with concentric geometry were age, night-time SBP values, and OSA (Table 3). In the multivariate linear regression model, the factors independently associated with GLS were OSA and night-time DBP (Table 4), whereas factors independently associated with mwFS were age, night-time DBP, OSA, and metabolic syndrome (Table 5).

4. Discussion

Patients with RH have shown a significant increase in cardiovascular event risk during follow-up compared with non-RH patients [4]. It may be related to more pronounced subclinical cardiac damage

Table 2
Left ventricular morphofunctional characteristics among the four groups.

Variables	Group 1 ($n = 42$)	Group 2 ($n = 14$)	Group 3 ($n = 46$)	Group 4 ($n = 53$)	ANOVA
IVSDd (mm)	11.1 ± 1.6	12.7 ± 1.4[a]	12.0 ± 1.6[b]	13.0 ± 1.6[c,d]	<0.0001
PWDd (mm)	10.9 ± 1.5	12.3 ± 1.2[a]	11.9 ± 1.4[b]	12.8 ± 1.4[c,d]	<0.0001
RWT	0.43 ± 0.06	0.47 ± 0.06	0.47 ± 0.07	0.52 ± 0.08[c,d]	<0.0001
LVMI (g/m^2)	116.6 ± 30.1	129.9 ± 20.4	122.4 ± 24.5	130.3 ± 29.7	0.09
LVH (%)	38.1	50.0	48.9	59.3	0.24
LVEF (%)	70.1 ± 4.8	70.6 ± 3.7	69.1 ± 4.9	69.1 ± 5.5	0.63
mwFS (%)	17.4 ± 1.9	16.4 ± 2.1	16.4 ± 1.9[b]	15.4 ± 2.2[c]	<0.0001
GLS (%)	−15.6 ± 4.0	−14.8 ± 4.1	−14.8 ± 3.3	−12.6 ± 3.3[c,d]	0.002

Abbreviations: ANOVA, analysis of variance; IVSDd, intraventricular septum diastolic diameter; PWDd, posterior wall diastolic diameter; RWT, relative wall thickness; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy in all groups; LVEF, left ventricular ejection fraction; mwFS, midwall fractional shortening; OSA, severe obstructive sleep apnea; GLS, global longitudinal strain.
Values are mean ± standard deviation, except for categorical variables.
[a] $P < 0.05$ group 2 vs group 1.
[b] $P < 0.05$ group 3 vs group 1.
[c] $P < 0.05$ group 4 vs group 1.
[d] $P < 0.05$ group 3 vs group 4.

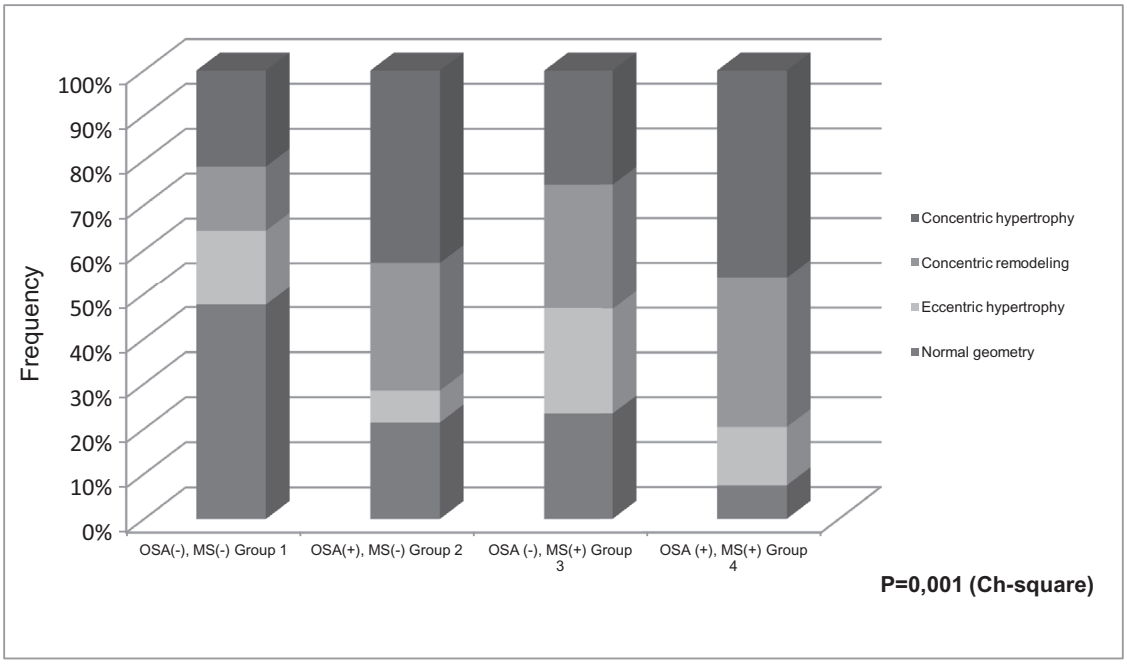

Fig. 2. Left ventricular geometry in the study population.

in patients with RH compared with those with well-controlled hypertension. The RESIST-POL study showed that OSA was present in 72.1% of patients with RH [13]. It is known that OSA leads to LVH and left ventricle dysfunction regardless of the effect of BP [6,19]. Because of the high prevalence of OSA in patients with RH and its influence on left ventricle morphology and function, the analysis of this group was extended by studying echocardiographic data.

Contradictory data exist regarding the link between OSA and LVM. Accordingly, some researchers proved that OSA is associated with the increase in LVM [20]. In contrast, Davies et al. did not find any significant differences in LVM between patients with OSA, non-apneic snorers, as well as age-, sex- and BMI-matched controls [21]. In the present study, no statistically significant differences in LVMI were found between the analyzed groups.

Noda et al. found that 50% of patients with AHI >20/h had LVH, in contrast to 30.5% of the patients with AHI <20/h. It is noteworthy that all patients with LVH had hypertension [9]. Furthermore, the authors found that 70% of the patients with severe OSA (AHI >30) and hypertension had LVH. In our study, 59.3% of the patients with OSA (AHI >15) and MS had LVH.

Concentric geometry increases the risk of cardiovascular diseases and general mortality [17]. In the study by Cioffi et al., the prevalence of concentric geometry in groups without and with mild OSA was similar (20% vs 12%), with no differences in BP values between the groups [8]. However, concentric geometry was significantly more frequent in patients with moderate and severe OSA (58%). Usui et al. found that only coexistence of severe OSA and MS was associated with increased prevalence of concentric hypertrophy [22]. In our study, 71.5% of the OSA patients without MS and 79.6% of the patients with OSA and MS had concentric geometry. Therefore, we suggest that presence of OSA has a significant impact on LV concentric geometry in patients with RH. This may be supported by the results of Cuspidi et al., who showed predominance of eccentric hypertrophy in patients with well-controlled hypertension, compared with predominance of concentric hypertrophy in patients with RH [23]. Such a high prevalence of concentric geometry in patients with RH and OSA from our study places this group at a higher risk of cardiovascular complications. Pedrosa et al. demonstrated that the diagnosis and treatment with CPAP may positively impact on cardiac remodeling in RH patients with coexisting OSA [24]. This has major clinical value because change in cardiac geometry may decrease the number of cardiovascular events in this group of patients.

No data regarding LV systolic function in patients with RH are available. Patients with hypertension have, most usually, preserved LVEF [10]. This parameter reflects endocardial displacement

Table 3
Univariate and multivariate logistic regression model for the variables associated with concentric geometry (relative wall thickness >0.45).

Variables	Univariate model			Multivariate model		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.71	1.227–2.368	0.001	1.04	1.006–1.082	0.023
Sex	1.15	0.597–2.202	0.68			
Night-time SBP	1.04	1.021–1.068	<0.0001	1.04	1.019–1.082	<0.0001
Metabolic syndrome	2.58	1.312–5.985	0.006			
OSA	4.27	2.094–8.715	<0.0001	3.97	1.835–8.590	<0.0001
24 h urinary sodium excretion	0.80	0.404–1.581	0.52			

Abbreviations: OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; OSA, severe obstructive sleep apnea. Multivariate model included: age, gender, night-time SBP, metabolic syndrome, obstructive sleep apnea (OSA) and 24 h urinary sodium excretion.

Table 4
Univariate and multivariate linear regression model for factors associated with global longitudinal strain.

Variables	Univariate model		Multivariate model	
	β	*P*	β	*P*
Age	0.192	0.028	0.138	0.11
Sex	0.244	0.005	0.147	0.12
OSA	0.279	0.001	0.279	0.001
Night-time DBP	0.198	0.024	0.168	0.048
Metabolic syndrome	0.223	0.011	0.130	0.14
24 h urinary sodium excretion	−0.120	0.17		

Abbreviations: OSA, severe obstructive sleep apnea; DBP, diastolic blood pressure. Multivariate model included: age, gender, obstructive sleep apnea (OSA), night-time DBP, metabolic syndrome, and 24 h urinary sodium excretion.

and is not suitable for the assessment of systolic function in cases of LV concentric remodeling or of hypertrophy. In patients with OSA, data regarding systolic function are inconsistent [20,25]. Although many studies showed a normal systolic function, they are all limited to the assessment of LVEF [26].

de Simone et al. proposed assessing of mwFS of the myocardial layer [18], which is superior, and evaluating the systolic function in patients with thicker myocardial walls. Consequently, we measured the systolic function by mwFS. The lowest values of mwFS were noted in patients with MS and OSA. This is in agreement with the results of Ciofii et al. who found that patients with moderate and severe OSA have LV systolic dysfunction measured by mwFS [27]. Considering the impact of MS on LV systolic function, Mule et al. in line with our study documented lower mwFS in patients with MS, compared with those without MS [28]. Additionally, we found that OSA, age, MS, and night-time DBP were independent factors associated with mwFS. This leads to the conclusion that OSA and MS may have an additive effect to RH on LV systolic dysfunction.

Speckle-tracking echocardiography is a novel technique for quantitative assessment of systolic function. It allows for local and global myocardial strain measurement. In a recent study, Altekin et al. showed lower global longitudinal strain (GLS) in patients with OSA than that in healthy subjects [12]. AHI was significantly correlated with GLS. Vitarelli et al. found dysfunction of longitudinal fibers using STE in patients with OSA who had preserved LVEF when compared with healthy subjects [11]. Additionally, MS has an impact on systolic function measured by STE. Gong et al. compared a group of patients without MS with those having three or four components of MS, and found a significant decrease in GLS among patients with MS, which was related to the number of components [29]. In our study, we documented the lowest value of GLS in patients with OSA and MS. However, in the multivariate model, MS in contrast with OSA and night-time DBP was not an independent factor associated with GLS. It is worth noting that, in the last European Society of Cardiology guidelines for the management of hypertension, strain has been implemented into the evaluation of left ventricular systolic function [30]. Our results confirm the usefulness of STE for the early discovery of left ventricular systolic dysfunction in patients with resistant hypertension.

Table 5
Univariate and multivariate linear regression model for variables associated with midwall fractional shortening.

Variables	Univariate model		Multivariate model	
	β	*P*	β	*P*
Age	−0.268	0.001	−0.186	0.013
Sex	−0.169	0.036	−0.082	0.49
OSA	−0.300	0.0001	−0.200	0.009
Night-time DBP	−0.319	0.0001	−0.292	<0.0001
Metabolic syndrome	−0.301	0.0001	−0.240	0.001
24 h urinary sodium excretion	0.024	0.77		

Abbreviations: OSA, severe obstructive sleep apnea; DBP, diastolic blood pressure. Multivariate model included: age, gender, obstructive sleep apnea (OSA), night-time DBP, metabolic syndrome, and 24 h urinary sodium excretion.

Studies reinforcing the position of ABPM, particularly BP levels during the night, in predicting cardiovascular risk have been published [1,31]. The Spanish registry database analysis included 2115 patients with treated hypertension and high or very high cardiovascular risk. It showed that BP values in ABPM are independently and significantly associated with the risk of cardiovascular event [1]. The systolic BP values during the night had the strongest predictive value in this analysis. Cuspidi et al. evaluated patients with increased nocturnal BP levels in ABPM and found no differences in target-organ complications between patients with and without BP fall during the night. The authors suggest that this may indicate a significant relationship between absolute nocturnal BP values (not between its relative decrease in relation to BP values during the day) and target-organ complications [31].

No studies have addressed the impact of nocturnal BP levels and night-to-day BP fall on the left ventricular mass and function in patients with RH. In our study, night-time SBP and DBP were significantly correlated with LVMI and RWT. Interestingly, neither decrease nor increase in night-time SBP and DBP were significantly correlated with LVMI. Night-time SBP was a significant factor independently associated with concentric geometry in the multivariate regression model. Our results suggest that nocturnal BP levels have an impact on concentric geometry.

Most of the published studies analyzed the impact of mean 24 h BP levels on left ventricle systolic function. The importance of nocturnal BP levels in this respect remains unknown. When assessing endocardial fractional shortening (SF) in dippers and non-dippers, Cuspidi et al. found no significant differences in systolic function between these groups [32]. In our study, night-time DBP was a factor independently associated with decreased GLS and mwFS. Thus, these results show that increased night-time DBP values lead to systolic dysfunction.

In conclusion, the major finding of our study is that, in the group of patients with true RH without diabetes, concentric geometry and systolic dysfunction are independently associated with moderate and severe OSA and night-time BP levels. Since we found the association between OSA and systolic dysfunction based on the evaluation of mwFS and GLS but not LVEF, we postulate that the assessment of systolic function in this population should also be based on the mwFS and GLS.

Since concentric geometry and systolic dysfunction are known to contribute to increased cardiovascular risk, in patients with RH attention should be focused on OSA detection and treatment, in order to prevent further cardiac damage. Further studies employing long-term follow-up are necessary to confirm our findings.

There are several limitations to the present study. Since consecutive patients with true RH were enrolled, the relatively small number of patients with OSA without metabolic syndrome (group 2) reflects the prevalence of OSA not accompanied by metabolic syndrome.

Only middle aged or younger subjects with preserved renal function and without a history of diabetes were included in the study, thus mitigating the potential confounding effects of advanced age and comorbidities in our results. Therefore, our results may not be applicable to a wider population of patients with true RH.

The cross-sectional design did not enable determination of a cause–effect relationship between RH, OSA, and MS and developmental changes of left ventricle geometry and systolic function. One technical limitation is that STE is dependent both on frame rate and image resolution [33]. Thus, in the presence of obesity and OSA, it may be challenging to acquire views of good quality. We overcame

this limitation by assessing GLS only in a four-chamber view, which was characterized by best left ventricle wall definition and image resolution. Despite this limitation we succeeded in testing our hypothesis that GLS is more accurate in assessing early changes in left ventricle systolic function.

Conflicts of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.06.015.

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